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Safety of antiepileptic drugs in children and young people: A prospective cohort study

Oluwaseun Egunsola[a,*], Imti Choonara[a], Helen M. Sammons[a], William P. Whitehouse[b]

[a] Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Derby, DE22 3DT, UK
[b] School of Medicine, University of Nottingham and Department of Paediatric Neurology, Nottingham Children's Hospital, Nottingham University Hospitals' NHS Trust, Nottingham, NG7 2UH, UK

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ABSTRACT

Purpose: This study aims to describe the incidence of adverse drug reactions (ADRs) in children receiving antiepileptic drugs (AEDs) and compare ADRs to the individual drugs when given as monotherapy.
Method: Paediatric patients (≤18 years old) were enrolled for this prospective observational study over a 6-month period, between September 2015 and March 2016. Adverse reactions to antiepileptic drugs (AEDs) were elicited at the time of enrolment and after 3 months using the Paediatric Epilepsy Side Effects Questionnaire.
Results: A total of 1139 suspected ADRs were reported in 124 participants. Eighteen different AEDs were prescribed. Sixty-six children (53%) were receiving AED monotherapy at the time of recruitment; 34/66 (52%) of whom received new generation AEDs. Levetiracetam was the most frequently prescribed AED (62/124, 50%). When only children receiving AED monotherapy were considered, fatigue, drowsiness, weight gain, dizziness were less likely with levetiracetam ($p < .01$). Slow thinking and decreased concentration were less likely with levetiracetam or carbamazepine than valproic acid ($p < .05$). Five patients (four on polytherapy) discontinued AED treatment due to ADRs and 2 had a dose reduction.
Conclusions: Levetiracetam and carbamazepine were better tolerated than sodium valproate.

1. Introduction

Adverse drug reactions (ADRs) are common causes of antiepileptic drug (AED) treatment failure. Up to 25% AED treatment failure has been attributed to ADRs [1,2]. They can be dose dependent or idiosyncratic. Dose dependent drug reactions worsen with increasing dose and often occur at the initiation of treatment. They are more likely to occur in patients in whom the AED dose has been aggressively escalated and can prevent the attainment of fully effective doses, as well as reduce patients' adherence [2]. Idiosyncratic reactions are unpredictable and often require AED treatment discontinuation [3]. Furthermore, children exposed to multiple AEDs are predisposed to ADRs arising from drug–drug interactions [4,5]. In about 30% of children, epilepsy is often drug resistant and a change in treatment or addition of new AEDs is indicated [6].

The goal of epilepsy treatment is seizure control while minimising AED ADRs. A recent UK clinical audit of epilepsy identified lack of sufficient information on ADRs as one of the most common areas for improvement in epilepsy care in children [7].

Information on AED safety is mainly derived from clinical trials, which are often not designed to provide sufficient drug safety information. Very few prospective AED safety studies [8–10] have been carried out in children and comparative primary safety studies are lacking.

With the increasing use of new AEDs, there is a greater need to determine and compare the safety of these drugs, especially with the more established old generation drugs. Several of the newer AEDs do not have superior efficacy to the older drugs, and their relative safety, based on the available evidence, is their only comparative advantage [11]. When comparative efficacies are similar, drug choice is often based on local preference or safety profile [12]. While there are several safety studies of the older agents; our knowledge of the safety profiles of the newer drugs is inadequate, mainly because of the relatively small number of patients exposed to some of these drugs. Furthermore, safety evaluation of the new drugs during the immediate post marketing period has also been challenging, as they were mostly approved as add-on treatments and often have restricted use in children.

In this study, the incidence of ADRs in children receiving AED treatment will be described. In addition, the ADRs to the individual

* Corresponding author at: Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Derby, DE22 3DT, UK.
E-mail address: oluwaseun.egunsola@sydney.edu.au (O. Egunsola).

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drugs as well as the ADRs to the drugs as monotherapy or polytherapy will be compared.

2. Methods

2.1. Participants

Participants were enrolled for this prospective observational study over a 6-month period, between September 2015 and March 2016. All children and adolescents aged ≤18 years, attending paediatric and teenagers' outpatient epilepsy clinics at the Queens Medical Centre, Nottingham, UK were eligible for inclusion. Only participants receiving one or more AEDs for any type of epilepsy were included in the study. Written informed consent was obtained from parents or guardians of participants less than 16 years old at the time of clinic appointment. However, written consent was sought directly from participants 16 years old and over. The study was approved by the North West – Greater Manchester Central Research and Ethics Committee (Reference number: 12/NW/0868).

2.2. Study outcomes

The primary study outcomes were to describe the incidence of ADRs for each AED and compare their toxicity. The secondary outcome was to compare the toxicity of individual AEDs when given as monotherapy and polytherapy. The methodologies for ADR data collection and evaluation will also be piloted for a planned national study.

2.3. Data collection and follow-up

Baseline data were recorded, by a member of the research team-OE, on a case report form at the point of recruitment. Data sources were primarily the participants' hospital case notes and electronic records. Data collected included: hospital number, date of birth, gender, weight, AED(s), dose of AED(s), other drugs, type of epilepsy, presence of intellectual disability, e-mail address or postal address and date of visit.

ADRs were elicited at the time of enrolment using the Paediatric Epilepsy Side Effects Questionnaire [13]. The parents or guardians were required to complete this questionnaire if the child was less than 13 years old or had learning difficulties. Older children could complete the questionnaire alone or together with their parents or guardian. It consisted of 19 specific questions on possible ADRs of AEDs and a general enquiry section, which allowed participants to report other ADRs. It also allowed participants or their parents/guardian to rate the severity of the ADRs using a Likert scale between 1 and 5, with 1 corresponding to low severity and 5 to high severity. The participants were asked to identify and rate any ADR experienced in the preceding 3 months. All participants were sent a follow-up questionnaire electronically or by post, 3 months after enrolment. Thus, a total of 6 months of follow-up data was generated. If the participant or parent did not respond to the initial email, a reminder was sent one week later.

2.4. Causality assessment

The relationship between AEDs and suspected ADRs was established using the Liverpool Adverse Drug Reaction Causality Assessment Tool [14]. This algorithm categorises suspected ADRs as unlikely, possible, probable and definite, based on a series of questions on a flow chart.

2.5. Statistical analysis

Antiepileptic drugs ADRs were compared using Chi^2 analysis or Fischer's exact test where appropriate. For all statistics, p values $< .05$ were considered statistically significant. SPSS version 22 was used for all analyses.

3. Results

3.1. Study characteristics

A total of 124 participants were recruited into the study and all completed the first questionnaire. About one quarter of the participants completed the follow-up questionnaire. Of the 98 participants that received the second questionnaire electronically 3 months after recruitment, only 27 (28%) responded. Similarly, 25% (6 participants) of the 24 participants who received the second questionnaire by post responded. Two participants opted not to receive follow-up questionnaires. The majority of the participants were male 56% (n = 70). The median age of participants was 10 years [range: 3 months-18 years; IQR: 6–14]. Twenty-eight participants had intellectual disability (Table 1). Forty-five patients (36%) were classified as having structural focal epilepsies, 31 (25%) with unclassified focal epilepsies and 18 (15%) with genetic generalised epilepsies (Table 2).

3.2. Antiepileptic drug therapy

Eighteen different AEDs were prescribed either as monotherapy or polytherapy. Sixty-six children (53%) were receiving AED monotherapy at the time of recruitment; 34/66 (52%) of whom received new generation AEDs (levetiracetam, lamotrigine, topiramate and zonisamide), and 32/66 (48%) received old generation drugs (sodium valproate, carbamazepine and clobazam). Most children on polytherapy received 2 AEDs (38/58; 66%). Levetiracetam was the most frequently prescribed AED, with 62/124 (50%) children receiving the drug as either monotherapy or polytherapy. More than half (34/62; 53%) of the participants receiving levetiracetam had polytherapy. Sodium valproate (42/124; 34%), clobazam (28/124; 22%), carbamazepine (22/124; 18%) and lamotrigine (19/124; 15%) were the other frequently prescribed AEDs (Fig. 1).

Table 1
General characteristics.

Characteristics	Number
Number of participants	124
Number of participants with suspected ADR	108
Number of suspected ADRs	1139
Median number of suspected ADRs	8 [IQR: 3–12]
Median age (years)	10 [IQR: 6–14.5]
Participants with intellectual disability	28 (23%)
Participants with ADHD	5 (4%)
Gender	
Male	70 (56%)
Female	54 (44%)
Regimen	
Monotherapy	66 (53%)
Polytherapy	58 (47%)
2 AEDs	38
3 AEDs	17
4 AEDs	2
5 AEDs	1
Severity of suspected ADRs	
Low	577 (51%)
Moderate	393 (34%)
High	152 (13%)
Unknown	17 (2%)